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Title page

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Role of surgical resection for patients with recurrent or metastatic gastrointestinal stromal tumors: a systematic review and meta-analysis

Abstract

Background: The role of surgical resection for patients with recurrent or metastatic gastrointestinal stromal tumors is still controversial. This meta-analysis aims to investigate the clinical outcomes of surgery combined with tyrosine kinase inhibitors among patients with recurrent or metastatic gastrointestinal stromal tumors.

Methods: We systematically searched PubMed, EMBASE, the Cochrane Library and Wanfangdata without language restriction. Random effect models were used to estimate pooled hazard ratio and the corresponding 95% confidence intervals. Subgroup analyses, sensitivity analysis and trim and fill analysis were also performed.

Results: A total of 1416 patient from 9 studies were finally enrolled in this meta-analysis. The summary results showed that surgery combined with tyrosine kinase inhibitors showed a tendency of a longer overall survival compared with tyrosine kinase inhibitors treatment alone (HR by random-effects model 0.68, 95% CI 0.54-0.85, I^2 = 44.7 %) and improved progress-free survival (HR by random-effects model 0.50，95% CI, 0.33-0.76, I^2= 17.9%). The trim and fill analysis and sensitive analysis indicated the relatively robust result.

Conclusion: Surgery combined with tyrosine kinase inhibitors therapy is associated with a better overall survival and progression free survival for patients with recurrent or metastatic gastrointestinal stromal tumors as compared with TKIs treatment alone.

Keywords: gastrointestinal stromal tumors; GISTs; surgery; metastatic; recurrent;

1. Introduction

Gastrointestinal stromal tumors (GISTs) which originate from interstitial cells of Cajal are the most common mesenchymal neoplasms of the gastrointestinal tract.[1] Most GISTs have an activating mutation in gene encoding KIT or platelet-derived growth factor receptor alpha (PDGFRA) receptor tyrosine kinase;[2,3] therefore tyrosine kinase inhibitors (TKIs) such as imatinib mesylate (IM) and sunitinib malate(SU) are used for GISTs with activated KIT or PDGFRA in vitro. The introduction of TKIs significantly improved clinical outcomes for patients with the metastatic or recurrent disease.[4–8]However, after an initial benefit from TKIs, many patients eventually develop disease progression or secondary resistance on account of acquired mutations in KIT or PDGFRA.[3,9,10] Thus various treatment strategies including the operative therapy combined with TKIs, resumption of IM, IM dose escalation or treatment with other targeting agents have been investigated to improve the prognosis of patients with recurrent or metastatic GISTs.[5,6,11–14]

Metastatic and recurrent disease were commonly seen in patients with GISTs. The benefits of surgery, once the cornerstone of treatment for patients with localized GISTs,[15,16] are still in discussion for patients with recurrent or metastatic gastrointestinal stromal tumors. Several retrospective studies have demonstrated surgical resection of GISTs combined with TKIs might be beneficial for patients with recurrent or metastatic GIST,[14,17–25] which may result from the assumption that surgery reduces the tumor burden and delays the time to the development of secondary resistance to TKIs therapy, contributing to a better prognosis.[26,27] On the contrary some conflicting data regarding the role of operation in

recurrent or metastatic diseases have also been reported in term of overall survival(OS) or progression-free survival(PFS).[28–30] Therefore, it is necessary to perform a systematic and comprehensive meta-analysis to reassess the role of surgery combined with TKIs in patients with recurrent or metastatic GISTs.

In the present study, a meta-analysis was conducted to clarify the association between survival outcomes and two treatment therapies—TKIs with surgery and TKIs treatment alone in patients with recurrent or metastatic GISTs and explores potential sources of heterogeneity across di□erent studies.

2. Methods

2.1 Search Strategy

Two investigators performed a systematic literature search in PubMed, EMBASE, Cochrane Library, and Wanfangdata (last updated on September 27, 2017), using combinations of the following terms: “gastrointestinal stromal tumors”, “GIST”, “GISTs”, “surgery”, “recurrence”, “metastasis”, “metastasectomy”, no language restrictions were applied and conference abstracts were excluded due to the insufficient data reported. The reference list was also checked for relevant studies and all studies were carefully evaluated to identify duplicate data.

2.2 Inclusion criteria

The following criteria were used for the study selection: (1) Participants (P): Patients who were histologically confirmed with recurrent and/or metastatic gastrointestinal stromal tumors according to the histologic examination and CD117, CD34, or PDGFRA positivity. (2) Interventions (I) and comparisons

(C): surgical resection plus TKIs versus TKIs therapy alone. (3) Outcomes: OS or PFS. (4) Study design (S): Observational cohort studies and randomized controlled studies(RCTs). (5): Provided enough information to estimate hazard ratio (HR) and 95% confidence intervals (CIs). Meeting abstracts, letters, case reports, reviews or nonclinical studies without usable data were excluded.

2.3 Qualitative assessment and data extraction

The quality of the non-randomized studies was estimated by two investigators using the Newcastle Ottawa quality assessment scale (NOS),[31] NOS scores of ≥ 6 were assigned as high-quality studies and the risk of bias of randomized controlled trials was assessed by Cochrane Collaboration's tool.[32]

Two investigators independently extracted the required information which includes the number of patients, year of publication, first author, country, follow-ups and results regarding survival benefit (OS and PFS) from all primary studies, which ensures homogeneity of data collection.

2.4 Statistical analysis

PRISMA checklist[33] was used as the guideline for the meta-analysis. Taking the number and timing of events into consideration, hazard ratios (HRs) are used to assess time-to-event outcomes and we obtained the data directly from the studies or used Kaplan–Meier survival curves to estimate necessary statistics which is reported by Tierney et al.[34] A HR >1 indicated a worse prognosis in patients with metastatic or recurrent GISTs. Heterogeneity of the included trials was assessed by Cochran Q test and measured by the I^2 statistic and interpretation of the I^2 values was made by assigning attributes of low, moderate, and high in

case of 0–25%, 25–50% and above 75%, respectively.[35] The pooled HRs and 95%CIs were calculated by random effects DerSimonian–Laird method models. Subgroup analysis was performed to explore and explain the diversity (heterogeneity) among the results of different studies according to study design, sample size, ethnicity, survival analysis, and mean follow-up was used to assess the publication bias. The analysis of publication bias by Begg's funnel plot and Egger regression was not conducted for the reason that the number of enrolled studies was less than ten.[36–38] Trim-and-fill analysis was conducted to explore the potential of publication bias from our studies.[39] STATA version 14.0 (STATA, College Station, TX) was used to analyse the relevant statics. The statistical tests were two-sided, and P values less than 0.05 were considered statistically significant.

3. Results

3.1 Study selection and characteristics

A total of 5634 articles were identified with the search strategy designed and conducted by a medical librarian from various databases including PubMed, EMBASE, Cochrane Library, Wanfangdata, of which 4594 were considered potentially relevant articles after excluding duplicate articles and screening the titles and abstracts. A further 4563 records were excluded for not relevant studies, reviews, conference abstract, etc. After assessing the remaining 31 articles by full-text review, 22 articles were excluded; of these, 8 were excluded due to the insufficient reported data for the estimation of HR, 3 was excluded for duplicate data, and 11 were excluded due to the shortage of TKIs therapy alone group. Finally, a total of 9 studies[17,19,21,22,28,30,40–42] were included in this meta-analysis. Literatures screening process was

shown in Figure 1.

The characteristics of included studies are shown in Table 1, of which eight studies were conducted in Asia, one in Spain. The outcomes were OS in 9 studies and PFS in 3 studies. The recurrent or metastatic GISTs reported in 2 studies were all relapses after surgery.

The scores of observational cohorts assessed by Newcastle-Ottawa quality assessment scale were all above 6, indicating high value indicating eligible methodology.

3.2 Overall survival

All Nine studies including 1416 GIST patients assessed OS. Surgery combined with TKIs showed a tendency of a longer OS compared with TKIs treatment alone (HR by random-effects model 0.68, 95% CI 0.54-0.85, I^2 = 44.7 %, Figure 2). Subgroup analyses by study design (RCT, observational studies) assured the role of surgery combined with TKIs in the observational studies (HR by random-effects model 0.61, 95% CI 0.43–0.87; I^2 = 48.9 %) and get a statistically non-significant trend to better survival as compared with TKIs treatment alone. from two small sample RCTs (HR by random-effects model 0.75, 95% CI 0.53–1.04; I^2 = 47.7 %). Subgroup analyses were also conducted to explore the source of heterogeneity. When stratified by sample size (≥100 and <100), we got statistical significance from both groups. Besides, subgroup analysis was also performed by classification of recurrent or metastatic GISTs, ethnicity, mean follow-up and survival analysis(Table 2). Sensitivity analysis indicated that the study by Park, S. J. et al.[40] contributed most to the variability among all studies, pooled HR, however, did not vary substantially after omitting each of the nine studies, confirming the stability of present results. (Figure 3)

3.3 Progression-free survival

Three studies[17,19,40] presented the data of PFS that can be pooled for the meta-analysis. A random-effects model was used for estimating the pooled HRs for PFS. Our results revealed that surgery combined with TKIs indicated a better PFS (HR 0.50，95% CI, 0.33–0. 76, $p < 0.05$, $I^2 = 17.9\%$, $p = 0.296$, Figure 4).

3.4 Publication bias

The result of trim and fill analysis suggested that no trimming was performed and the unchanged data indicated the stability of our results. (Supplementary Material)

4. Discussion

Over the last decade, the outcomes for patients with GIST have dramatically improved since introduction of TKIs which allow most patients to lead a normal life for an extended period and prolong disease control, complete surgical resection followed by adjuvant TKI therapy also plays an important role in the standard management for patients with primary GIST.[43] In the TKIs era, however, the role of surgery combined with TKIs in metastatic or recurrent GIST is not yet established and the past few years have seen growing much debate on surgical resection combined with TKI. Therefore, we performed a systematic meta-analysis on this treatment's effect on the prognosis of the patients with metastatic or recurrent GIST.

As far as we know, the present study is the first meta-analysis of the association between prognosis and surgical resection combined with TKIs. Until a large sample RCT is done, the findings from this

meta-analysis are the best evidence available.

This meta-analysis included nine studies with 1416 GIST patients of which 351 were surgically treated. This study provided relatively robust evidence demonstrating that surgery combined with TKIs therapy was associated with improved outcomes as compared with TKIs treatment alone in terms of OS and PFS in patients with metastatic or recurrent GISTs. The pooled results from this meta-analysis confirmed that a benefit of OS for surgery combined with TKIs. In the subgroup of observational studies surgery indicated an improved OS, however subgroup analysis revealed that there was no significant di□erence of OS in the RCT group. The results were not substantially affected by subgroup analysis. Moreover, omission of any of the articles did not alter the magnitude of pooled observed effect and no trimming of data has been performed by trim-and-fill analysis suggesting stability of our findings. The pooled results from this meta-analysis also confirmed that surgery therapy could significantly impact PFS.

Studies suggested that whether patients responded to TKIs at the time of surgery was associated with the outcomes. Previous studies demonstrated that the tumor responsive to imatinib before resection was strongly correlated with improved OS or PFS.[14,20,25,44–47]. The benefits of metastasectomy for progressive tumor after TKIs therapy are still in discussion. Several studies found that patients who undergo surgery for the focal progressive disease have a limited benefit.[14][46] Some reports, however, showed that surgery improved the outcomes of patients with focally progressive GISTs resistant to TKIs.[17,48]

Based on the results of this meta-analysis, surgery combined with TKIs therapy is proved to be e□ective for patients with recurrent or metastatic GISTs. Therefore, we suggest that surgical resection and TKIs be combined for patients with metastatic or recurrent GISTs, and the final decision should be carefully made by the experienced multi-disciplinary team (MDT) taking into account of potential possible risks and

benefits to personalize treatment therapy to ensure maximum benefits.

Some limitations in our meta-analysis should be considered carefully. First, the total sample size is not very large, and several studies did not provide sufficient long-term follow-up time. Second, that only two small sample sizes RCTs were included in our meta-analysis may not be powerful enough to investigate the outcomes of the treatments, though the pooled results of the two RCTs also showed a trend to better survival as compared with TKIs treatment alone. Third, heterogeneity is a major issue that may affect the interpretation of the results of the meta-analysis. To address the issue of heterogeneity in OS, subgroup analyses were conducted. However, no e□ect modifier of heterogeneity was found. Fourth, for the limitation of meta-analysis of aggregate data from studies rather than individual patient data, it was difficult for us to extract, calculate and compare survival data in the subgroups by supposed predictors such as extent of tumor response to TKIs(partial response, disease progression, and stable disease), margin status, and metastatic organs. Bauer, S., et al.[49] reported that metastasis limited to the liver is associated with positive outcomes of surgical interventions compared with peritoneum and other sites of tumor involvement. However, several studies reported that resected organs did not show statistical difference regarding PFS or OS. As for resection margin, some reports[17,19] suggested margin-negative resection was strongly associated with improved PFS and the OS of patients with metastatic GISTs,[20,30,49] on the other hand Rubio-Casadevall, J. et al. reported that R0 resection was associated with a worse PFS compared with R1 and R2 resection.[19]

In conclusion, the findings of this meta-analysis suggest that surgery combined with TKIs therapy is associated with a better OS and PFS for patients with recurrent or metastatic gastrointestinal stromal tumors as compared with TKIs treatment alone. This association needs to be confirmed by more studies, especially

RCTs with larger sample sizes.

Conflict-of-interest statement:

We declare that we have no conflicts of interest.

Ethical statement:

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Figure legends

Figure 1. Flow chart of the study selection.

Figure 2. Meta-analysis and stratified analysis of hazard ratios of surgery combined with TKIs for overall survival (OS).

HR= hazard ratio, CI=confidence interval, I^2 = the percentage of total variation across studies that is due to heterogeneity rather than change, RCT= randomized controlled trial.

Figure 3. Sensitivity analysis. CI=confidence interval.

Figure 4. Meta-analysis and stratified analysis of hazard ratios of surgery combined with TKIs for progression free survival (PFS).

HR= hazard ratio, CI=confidence interval, I^2 = the percentage of total variation across studies that is due to heterogeneity rather than change.

Table 1 Characteristics of studies included in meta-analysis of role of surgery for patients with recurrent or metastatic gastrointestinal stromal tumors.

Study	Year	Region	Ethnicity	Study type	Follow-up (median, range)	Outcomes	Classification of recurrent or metastatic GISTs	Sample size			Median age	
								Total	Treated	Controls	Treated	Controls
Sato, S.	2017	Japan	Asian	Observational	75.2, 56.1–90.5	OS	Recurrence or metastasis after surgery	93	50	43	62.6	71
Hsu, J. T.	2017	Taiwan	Asian	Observational	NR	OS	NR	521	98	423	55.89	58.42
Shi, Y. N.	2017	China	Asian	Observational	48.2, 1-139	OS	Initially diagnosed metastatic GIST; Recurrence or metastasis after surgery	121	23	98	NR	NR
Gao, X.	2016	China	Asian	Observational	26,8–104	OS, PFS	NR	57	38	19	53	61
Rubio-Casadevall	2015	Spain	Caucasian	Observational	56.6	OS, PFS	NR	171	27	144	58.28	60.8
Park, S. J.	2014	Korea	Asian	Observational	58.9,15.4–129.1	OS, PFS	NR	134	42	92	51	58
Du, C. Y.	2014	China	Asian	RCT	NR	OS	Initially diagnosed metastatic GIST; Recurrence or metastasis after surgery	41	19	22	49	56
An, H. J.	2013	Korea	Asian	Observational	44.0,2.7–120.1	OS	Initially diagnosed metastatic GIST; Recurrence or	249	35	214	47	58

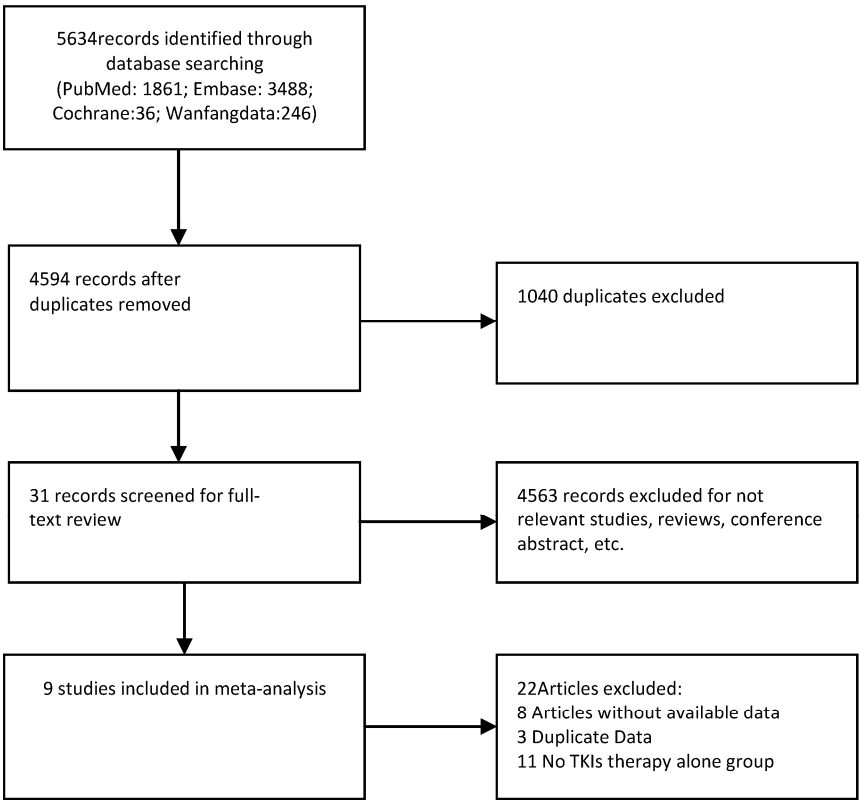
							metastasis after surgery					
Xia, L.	2010	China	Asian	RCT	NR	OS	Recurrence or metastasis after surgery	39	19	20	53	55

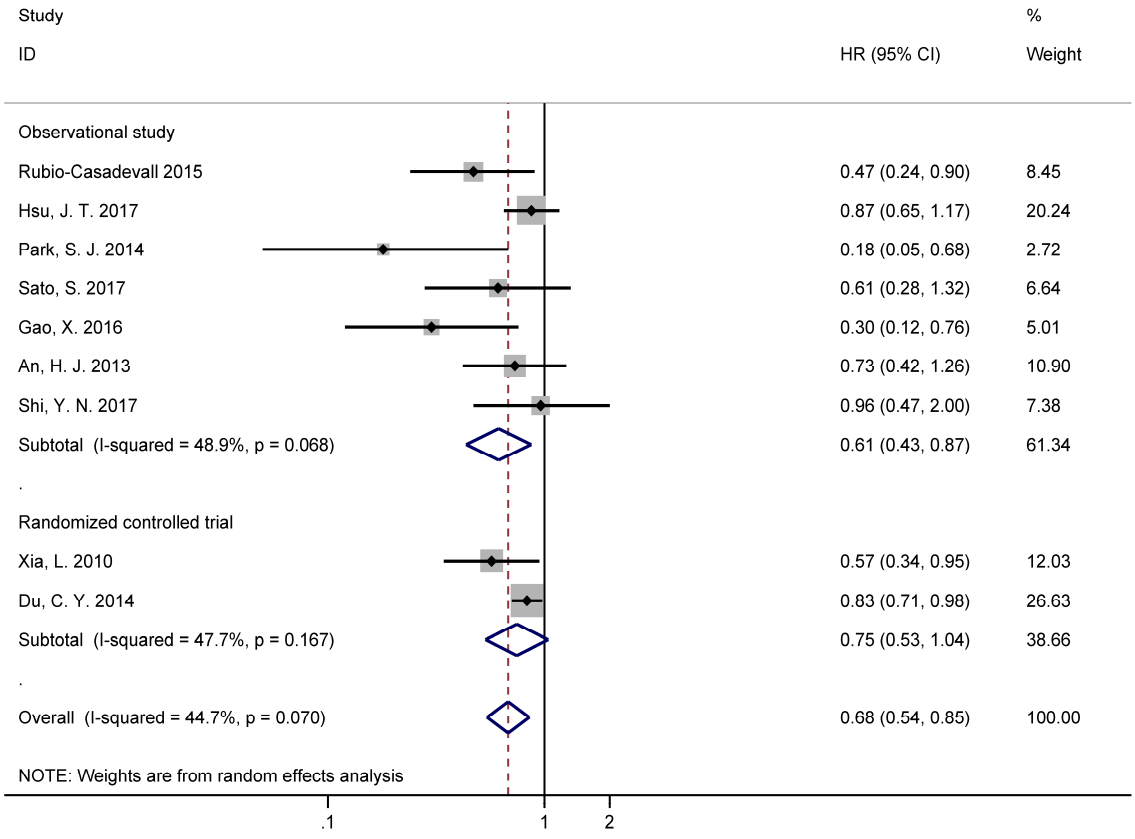
RCT= randomized controlled trial. OS= overall survival, PFS= progression-free survival, NR=not reported

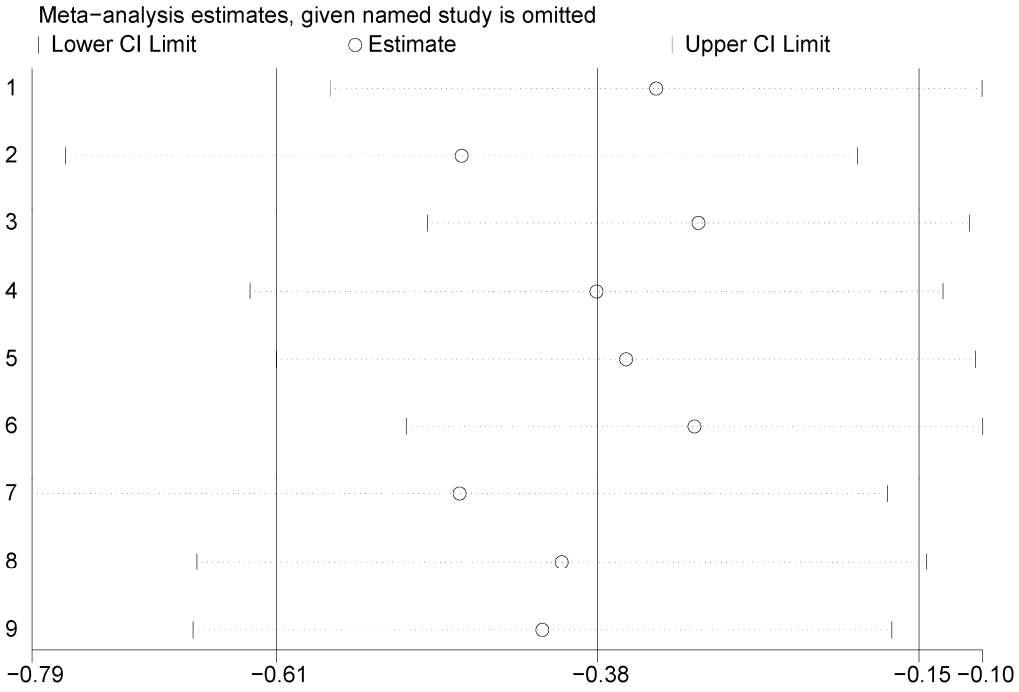
Table 2 Summary of meta-analysis results for role of surgery for patients with recurrent or metastatic gastrointestinal stromal tumors.

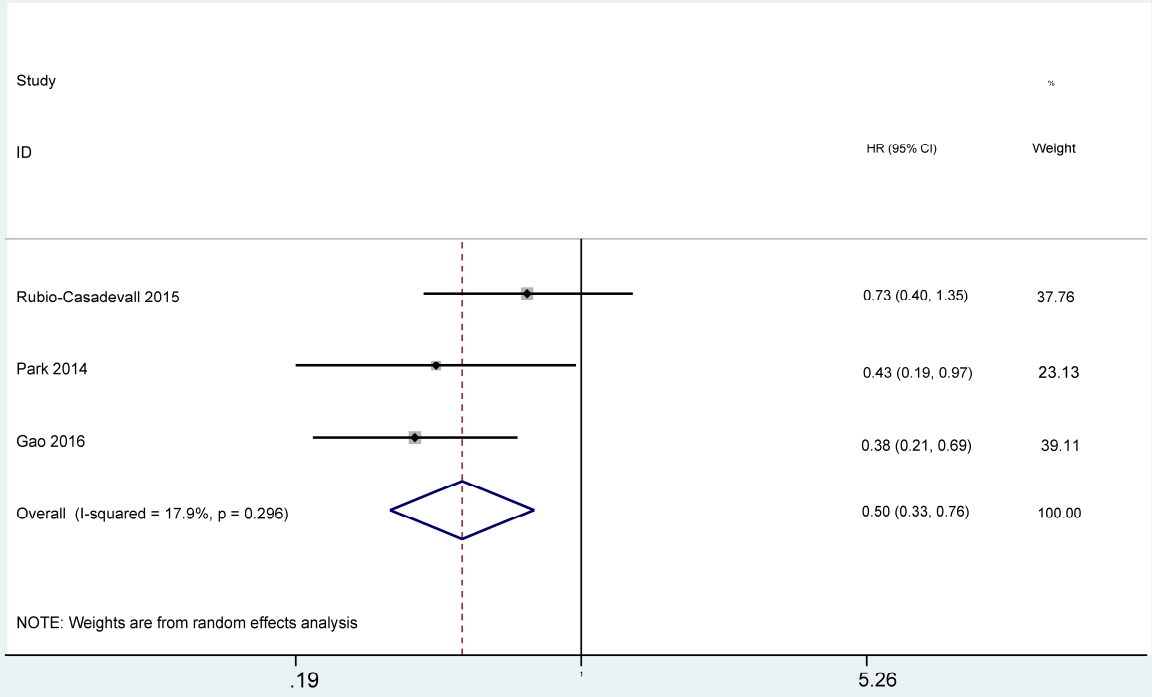
	Number of studies	Pooled estimated		Tests of heterogeneity	
		HR	95% CI	I^2 (%)	P value
All studies	9	0.68	0.54, 0.85	47.7	0.070
Studies design					
RCT	2	0.75	0.53, 1.04	47.7	0.167
Observational studies	7	0.61	0.43, 0.87	48.9	0.068
Sample size					
n ≥100	5	0.68	0.46, 0.99	49.6	0.094
n <100	4	0.63	0.43, 0.92	53.9	0.089
Ethnicity					
Asian	8	0.71	0.56, 0.89	42.9	0.070
Caucasian	1	0.47	0.24, 0.91	-	-
Survival analysis					
Cox regression	4	0.46	0.23, 0.93	72.4	0.012
Kaplan–Meier	5	0.79	0.69, 0.92	0	0.605
Mean follow-up					
Reported	6	0.54	0.37, 0.81	37.2	0.158
Not reported	3	0.81	0.70, 0.94	6.7	0.342
Classification of recurrent or metastatic GISTs					
Not all relapses after surgery	3	0.83	0.71, 0.96	0	0.834
Relapses after surgery	2	0.58	0.38, 0.89	0	0.886
Not reported	4	0.46	0.23, 0.89	72.4	0.012

HR= hazard ratio, CI=confidence interval, I^2 = the percentage of total variation across studies that is due to heterogeneity rather than change, RCT= randomized controlled trial.









Highlights

1. Gastrointestinal stromal tumors sometimes present as an advanced disease (including metastatic GISTs, local recurrence after initial resection, and combination of metastasis and recurrence).
2. Surgery combined with TKIs therapy is associated with a better overall survival and progression free survival compared with TKIs treatment alone for patients with recurrent or metastatic gastrointestinal stromal tumors.
3. The results need to be confirmed by more studies, especially RCTs with larger sample sizes.

International Journal of Surgery Author Disclosure Form

The following additional information is required for submission. Please note that failure to respond to these questions/statements will mean your submission will be returned. If you have nothing to declare in any of these categories then this should be stated.

Please state any conflicts of interest

None

Please state any sources of funding for your research

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This article does not contain any studies with human or animal subjects performed by any of the authors.

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Author contribution

Please specify the contribution of each author to the paper, e.g. study design, data collections, data analysis, writing. Others, who have contributed in other ways should be listed as contributors.

Bo Zhang and Zhaolun Cai designed the study. Sumin Tang and Xiaonan Yin searched and screened studies and extracted data. Zhaolun Cai and Yuan Yin did the statistical analyses and prepared figures. Bo Zhang, Zhixin Chen, Yuan Yin, Chaoyong Shen, Zhaolun Cai reviewed the results, interpreted data, and wrote the manuscript. All authors saw and approved the final version of the paper.

Guarantor

The Guarantor is the one or more people who accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Bo Zhang